Guidelines on Non-muscle invasive Bladder Cancer (TaT1 and CIS)

M. Babjuk, W. Oosterlinck, R. Sylvester,
E. Kaasinen, A. Böhle, J. Palou, M. Rouprêt

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1. BACKGROUND

1.1 Publication history

The first European Association of Urology (EAU) Guidelines on Bladder Cancer were published in 2002 (1). It was later decided to develop separate guidelines for different categories of urothelial tumours:

- TaT1 papillary tumours (non-muscle-invasive bladder cancer);
- Carcinoma *in situ* (CIS);
- Muscle-invasive bladder tumours;
- Upper urinary tract tumours.

Separate guidelines have been published in European Urology for TaT1, CIS, and upper urinary tract tumours (2-4). For logistical reasons, the guidelines group on non-muscle-invasive bladder cancer decided to integrate the guidelines of TaT1 tumours and CIS in one issue. This overview represents the updated EAU guidelines for non-muscle-invasive bladder cancer (CIS, Ta, T1).

1.2 Methodology

The systematic literature search for each section of the non-muscle-invasive bladder cancer guidelines was performed by the panel members. For identification of original and review articles, the Medline, Web of Science, and Embase databases were used. For the current upgrade, all articles published between 2008 and 2010 on TaT1 tumours and between 2004 and 2010 on CIS were considered. Focus of the searches was identification of all level 1 scientific papers (systematic reviews and meta-analyses of randomised controlled trials [RCTs]) in accordance with EAU methodology. Panel members rated papers following a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence (LE) (5). Additionally, recommendations have been graded (GR) to provide transparency between the underlying evidence and a recommendation given.

Table 1: Level of evidence*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

**Modified from Sackett et al. (5).*

It should be noted that when recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of RCTs may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Alternatively, absence of high level of evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences and costs when a grade is assigned (6-8).

The EAU Guidelines Office do not perform cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever this data is available, the expert panel will include the information.

Table 2: Grade of recommendation*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

**Modified from Sackett et al. (5).*

2. EPIDEMIOLOGY

Bladder carcinoma is the most common malignancy of the urinary tract. The worldwide age standardised incidence rate (ASR) is 10.1 per 100,000 for males and 2.5 per 100,000 for females (9). In Europe, the highest incidence (ASR) has been reported in the Western (23.6 in males and 5.4 in females) and Southern (27.1 in males and 4.1 in females) regions, followed by Northern Europe (16.9 in males and 4.9 in females). The lowest incidence is observed in Eastern European countries (14.7 in males and 2.2 in females) (10).

The global world mortality rate among males is 4 per 100,000 versus 1.1 per 100,000 among females. The ASR (per 100,000) only varies between 5.6 in developed countries and 3.1 in developing countries for males. For females the ASR varies between 1.4 in developed countries and 0.9 in less developed areas (9). In Europe, mortality rates show a substantial decline over the last decade of about 16% in men and about 12% in women (11).

Approximately 75-85% of patients with bladder cancer presents with a disease that is confined to the mucosa (stage Ta, CIS) or submucosa (stage T1). These categories are grouped as non-muscle invasive bladder tumours.

3. RISK FACTORS

Many of the aetiological factors for the development of bladder tumours are known and urologists should be aware of the types of occupational exposure that might be related to urothelial carcinogens (12-14). Aromatic amines were the first to be recognised. At-risk groups include workers in the following industries: printing, iron and aluminum processing, industrial painting, gas and tar manufacturing (LE: 3).

Another prominent risk factor is cigarette smoking, which triples the risk of developing bladder cancer (15-17) (LE: 2a). Smoking leads to a higher mortality rate from bladder cancer during long-term follow-up, even though, in a multivariate analysis, the prognostic effect of smoking was weaker than that of other factors, such as stage, grade, size and multifocality of the tumour (18).

4. CLASSIFICATION

4.1 Tumour, Node, Metastasis Classification (TNM)

The 2002 TNM classification approved by the Union International Contre le Cancer (UICC) has been widely accepted. This version was updated in 2009, but it has no changes for bladder tumours (Table 3) (19).

Table 3: 2009 TNM classification of urinary bladder cancer

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	CIS: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
	T2a Tumour invades superficial muscle (inner half)
	T2b Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:
	T3a Microscopically
	T3b Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
	T4a Tumour invades prostate, uterus or vagina
	T4b Tumour invades pelvic wall or abdominal wall
N - Lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)
M - Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

4.2 Histological grading of non-muscle-invasive bladder urothelial carcinomas

In 1998, a new classification of non-invasive urothelial tumours was proposed by the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) (1998 WHO/ISUP classification) and published by the WHO in 2004 (20,21) (Table 4). Its major contribution is a detailed histological description of the various grades, which uses specific cytological and architectural criteria. A website (www.pathology.jhu.edu/bladder) that illustrates examples of various grades has been developed to improve accuracy further in using the system.

Table 4: WHO grading in 1973 and in 2004 (20,21)

1973 WHO grading
Urothelial papilloma
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
2004 WHO grading
Flat lesions
Hyperplasia (flat lesion without atypia or papillary aspects)
Reactive atypia (flat lesion with atypia)
Atypia of unknown significance
Urothelial dysplasia, Urothelial CIS
Papillary lesions
Urothelial papilloma (which is a completely benign lesion)
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade papillary urothelial carcinoma
High-grade papillary urothelial carcinoma

The 2004 WHO classification of the flat lesions includes urothelial hyperplasia, reactive urothelial atypia, atypia of unknown significance, dysplasia and CIS. Among non-invasive papillary urothelial lesions, the 2004 WHO grading differentiates between PUNLMP and low-grade and high-grade urothelial carcinomas.

PUNLMPs are defined as lesions that do not have cytological features of malignancy but show normal urothelial cells in a papillary configuration. Although they have a negligible risk for progression, they are not completely benign and still have a tendency to recur. The intermediate grade (grade 2), which was the subject of controversy in the 1973 WHO classification, has been eliminated (22,23) (Figure 1).

It was shown that the 2004 WHO classification has a better reproducibility than the WHO 1973 classification (24).

The prognostic value of both grading systems (WHO 1973 and 2004) has been confirmed. Attempts to demonstrate better prognostic value of one system over another, however, have yielded controversial results (22-25). The majority of clinical trials published to date on TaT1 bladder tumours have been performed using the 1973 WHO classification, and therefore, the following guidelines are based on this scheme. Until the prognostic role of WHO 2004 is validated by more prospective trials, both classifications can be used.

Figure 1: Stratification of tumours according to grade in the WHO 1973 and 2004 classifications (26)*

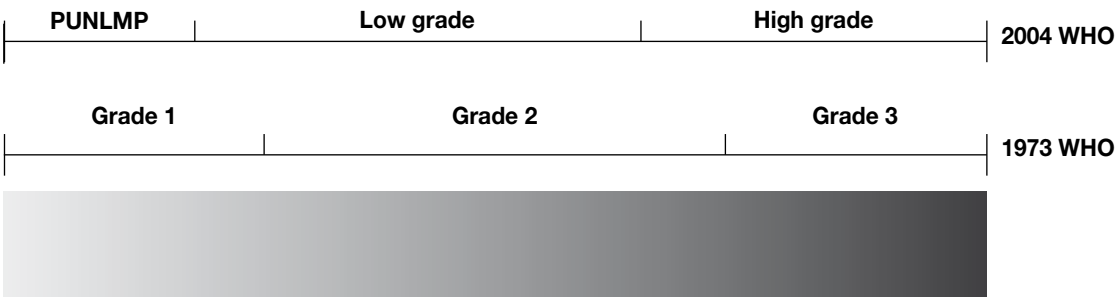


Fig. 1 - Comparison of the 1973 and 2004 WHO grading system. The 1973 WHO grade 1 carcinomas are reassigned, some to the PUNLMP category, and some to the low-grade carcinoma category. Similarly, 1973 WHO grade 2 carcinomas are reassigned, some to the low-grade carcinoma category, and others to the high-grade carcinoma category. All 1973 WHO tumors are assigned to the high-grade carcinoma category. WHO = World Health Organization; PUNLMP = papillary urothelial neoplasm of low malignant potential.

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4.3 Controversial definition of non-muscle-invasive ("superficial") tumours

The diagnosis of non-muscle-invasive bladder cancer requires consideration of all transurethral resection (TUR) samples.

A papillary tumour confined to the mucosa is classified as stage Ta according to the TNM system. Tumours that have invaded the lamina propria are classified as stage T1. Ta and T1 tumours can be removed by TUR, and therefore, they are grouped under the heading of non-muscle-invasive bladder cancer for therapeutic purposes. Also included under this heading are flat, high-grade tumours that are confined to the mucosa, and classified as CIS. However, molecular biology techniques and clinical experience have demonstrated the highly malignant, invasive potential of CIS and T1 lesions. Therefore, the terms non-muscle-invasive and superficial bladder cancer are suboptimal descriptions.

Some promising prognostic factors that are based on pathological examination of resected tissue have been presented:

- In patients with T1 tumours, the depth of invasion into the lamina propria is considered. The depth of invasion is evaluated in relation to the muscularis mucosae layer. T1 tumours are substaged into T1a (tumours that extend into the lamina propria but above the level of the muscularis mucosae) and T1b (tumours that infiltrate into or below the level of the muscularis mucosae). The prognostic value of T1 substaging has been demonstrated by some retrospective cohort studies (27-29) (LE: 3).
- The presence of lymphovascular invasion has been recognised as an unfavourable prognostic factor in T1 tumours (29,30) (LE: 3).
- Detection of the micropapillary variant of urothelial carcinoma represents a poor prognostic factor (31) (LE: 3).

4.4 Inter- and intra-observer variability in staging and grading

Despite well-defined criteria for the diagnosis of urothelial carcinoma, there is significant variability among pathologists for diagnosis of CIS, for which, agreement is achieved in only 70-78% of cases (32,33). There is also important inter-observer variability in classification of stage T1 versus Ta tumours, and grading tumours with general conformity between 50 and 60% (24,32-36). The inter-observer variability is less with the 2004 WHO classification compared to the 1973 classification (23,24). However, a review of slides is recommended particularly in T1, CIS and high-grade lesions.

4.5 Specific character of CIS and its clinical classification

Carcinoma *in situ* is a flat, high-grade, non-invasive urothelial carcinoma. The term CIS might suggest that it is a precursor of cancer. Although it might be a precursor of invasive bladder cancer, the histological and cytological aspects of CIS make this an overtly malignant entity in itself.

Macroscopically, CIS can be missed at cystoscopy or be considered as an inflammatory lesion if it is not biopsied. It is often multifocal and can occur in the upper urinary tract and in the prostatic ducts and urethra (37).

Carcinoma *in situ* is classified into one of three different clinical types (38):

- Primary: isolated CIS with no previous or concurrent exophytic tumours;
- Secondary: CIS detected during the follow-up of patients with a previous tumour;
- Concurrent: CIS in the presence of exophytic tumours.

5. DIAGNOSIS

5.1 Symptoms

Haematuria is the most common finding in non-muscle-invasive bladder cancer. TaT1 tumours do not cause bladder pain and rarely present with lower urinary tract symptoms. In patients who do complain of these symptoms, CIS might be suspected.

5.2 Physical examination

Physical examination does not reveal non-muscle-invasive bladder cancer.

5.3 Imaging

5.3.1 Intravenous urography and computed tomography

Intravenous urography (IVU) is used to detect filling defects in the calyces, renal pelvis and ureters, and

hydronephrosis, which can indicate the presence of a ureteral tumour. Large exophytic tumours may be seen as filling defects in the bladder. The necessity to perform routine IVU once a bladder tumour has been detected is now questioned because of the low incidence of significant findings obtained with this method (39-41) (LE: 3). The incidence of upper urinary tract tumours is low (1.8%), but increases to 7.5% in tumours located in the trigone (40). The risk of tumour recurrence in the upper urinary tract during follow-up increases in multiple and high-risk tumours (42).

In many centres, computed tomography (CT) urography is used as an alternative to conventional IVU (43). Especially in muscle invasive tumours of the bladder and in upper tract tumours, CT urography gives more information than IVU does (including status of lymph nodes and neighbouring organs) (LE: 4). However, CT urography has the disadvantage of higher radiation exposure compared to IVU.

*5.3.2 **Ultrasonography***

Ultrasonography (US) has been used with increasing frequency as the initial tool to assess the urinary tract. This is not only because it avoids the use of contrast agents, but also because sensitive transducers have improved imaging of the upper urinary tract and bladder.

Transabdominal US permits characterisation of renal masses, detection of hydronephrosis and visualisation of intraluminal masses in the bladder. It can be as accurate as IVU for diagnosis of upper urinary tract obstruction (39) (LE: 3). The US is thus a useful tool for investigation in patients with haematuria to detect obstruction, it cannot however exclude the presence of upper tract tumours. Imaging methods (IVU, CT urography or US) have no role in the diagnosis of CIS.

5.4 Urinary cytology

Examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in high-grade tumours but low sensitivity in low-grade tumours (LE: 2b). Due to a loss of cohesion of cells in the epithelial lining of the bladder in CIS, there is a larger number of floating cells in the urine, as well as a high degree of anaplasia. Thanks to these conditions is the sensitivity of cytology in CIS detection > 90%. Cytology is thus useful when a high-grade malignancy or CIS is present. However, urinary cytology often is negative in the presence of low-grade cancer. Positive voided urinary cytology can indicate a urothelial tumour anywhere in the urinary tract, from the calyx to the ureters, bladder and proximal urethra.

Cytological interpretation is user-dependent (44). Evaluation can be hampered by low cellular yield, urinary tract infections, stones or intravesical instillations. In experienced hands however, the specificity exceeds 90% (45) (LE: 2b). Cytology should be performed on fresh urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.

5.5 Urinary molecular marker tests

Extensive laboratory research has developed numerous urinary tests for diagnosis of bladder cancer based on detection of soluble or cell-associated markers (45-51).

Numerous reviews of urinary markers have appeared in recent years (45-59). A few of the markers have come into clinical application but none has been accepted as a standard diagnostic procedure in routine urology or in guidelines until now. Three tests are particularly promising: NMP22, UroVysion, and ImmunoCyt (49,50,60-64).

The following conclusions can be drawn about the existing tests. The BTA test has a very limited role because of its high false-positive rate and low sensitivity for low-grade tumours (65,66). NMP22 similarly suffers from a high false-positive rate but has higher sensitivity than urinary cytology. With careful selection of patients, the specificity of NMP22 can be improved, and because of its high negative predictive volume (NPV), it can potentially be used during follow-up to delay cystoscopy control (60,62,67-69). ImmunoCyt has the highest sensitivity for detection of low-grade tumours and is less affected by other urological diseases. However, with a 60% detection rate for low-grade tumours, the test remains largely inadequate to replace cystoscopy (64,70). UroVysion adds little to the surveillance of low-grade tumours. However, it can replace cytology for high-grade tumours when experience with urinary cytology is lacking or when its result is inconclusive, Some false-positive results arise because it can detect occult disease and thus identify those patients who are more likely to experience recurrence. It might also be useful to predict response to intravesical therapy (63,71,72). Microsatellite analysis was the most promising of the methods listed in Table 6. It can predict recurrence of low-grade tumours in up to 80% of cases, but it still lacks sensitivity (73-75).

The sensitivity of tests can be improved by their combination, as suggested by the International Consensus Panel on Bladder Tumour Markers (45).

Although it is hoped that these tests can soon make the transition from the laboratory to the clinic, it is essential to evaluate their costs to determine whether they can provide a low-cost and reliable alternative to current cystoscopy methods (76).

Table 5 gives an overview of how far the available urinary markers correspond to some of these criteria (52).

Table 5: Summary of main urinary markers

Markers	Overall sensitivity (%)	Overall specificity (%)	Sensitivity for high-grade tumours (%)	Point-of-care test	Interference by BCG instillations and other bladder conditions	Comments
UroVysion®	30-72	63-95	66-70	No	No	Expensive and laborious
Microsatellite analysis	58	73	90	No	No	Expensive and laborious
Gene microarray	80-90	62-65	80	No	No	Expensive and laborious
Immunocyt/ uCyt +™	76-85	63-75	67-92	No	Yes	Good sensitivity in low-grade tumours, affected by BCG
Nuclear matrix protein 22	49-68	85-87.5	75-83	Yes	Yes	Low sensitivity, affected by benign conditions
BTA stat	57-83	68-85	61.5	Yes	Yes	Low sensititivy, affected by benign conditions and BCG
BTA TRAK	53-91	28-83	77	No	Yes	Low sensitivity, affected by benign conditions and BCG
Cytokeratins	12-85	75-97	33-82	No	Yes	Low sensitivity, affected by benign conditions and BCG
Survivin	53-90	88-100	50	No	No	Low sensitivity, expensive and laborious

BCG = Bacillus Calmette-Guérin.

5.6 Practical application of urinary cytology and markers

There are specified general requirements for good markers for bladder cancer (45):

- The test must be as simple as possible technically (preferably a point-of-care test, with readily available results, easy to perform, with a short learning curve);
- Low cost;
- Reliable and reproducible results;

- High diagnostic accuracy (high sensitivity and specificity);
- For individual patient populations and clinical situations, the test should have a high positive predictive value to avoid unnecessary workup because of false-positive results, and high NPV to avoid the risk of failing to detect tumours. These parameters vary between populations with different incidences of bladder cancer and cannot be used for general comparison of methods;
- For clinical settings, it is of utmost importance to detect reliably all high-grade tumours before they escape curative treatment.

The following objectives of application of urinary cytology or molecular tests must be considered:

- *Screening of the population at risk of bladder cancer.*
  The application of haematuria dipstick, NMP22 or UroVysion in bladder cancer screening in high-risk populations has been reported (60,61). However, concerns about feasibility and cost-effectiveness mean that routine application of screening has not yet been established.

- *Exploration of patients after haematuria or other symptoms that are suggestive of bladder cancer.*
  It is generally accepted that none of the tests can replace cystoscopy. However, urinary cytology or markers can be used as adjunct to cystoscopy to detect invisible tumours, particularly CIS. In this setting, the method should have high sensitivity and specificity for high-grade tumours. Urinary cytology is highly specific and sensitive in this regard. Most commercially available urinary markers are even slightly more sensitive than cytology, the problem is however their lack of specificity.

- *Facilitate surveillance of non-muscle-invasive bladder cancer to reduce the number of cystoscopies (48,52,62,65).*
  To reduce the number of cystoscopies, urinary markers should be able to detect recurrence before the tumours are large and numerous. The limitation of urinary cytology is its low sensitivity for low grade recurrences. Several urinary markers are better but still do not detect half of the low-grade tumours that are detected by cystoscopy. Among the commercially available tests, the best performance for detecting recurrence of low-grade tumours is by immunocytology. Large prospective studies on recurrence of low-grade tumours are still lacking, thus, urinary markers cannot safely replace cystoscopy in this setting.

5.7 Cystoscopy

The diagnosis of bladder cancer ultimately depends on cystoscopic examination of the bladder and histological evaluation of the resected tissue. The diagnosis of CIS is made by a combination of cystoscopy, urine cytology, and histological evaluation of multiple bladder biopsies (77).

Cystoscopy is initially performed in the office, using flexible instruments. If a bladder tumour has been visualised in earlier imaging studies, diagnostic cystoscopy can be omitted because the patient will undergo TUR.

A careful description of the findings is necessary. It should include the site, size, number and appearance (papillary or solid) of the tumours, as well as a description of mucosal abnormalities. Use of a bladder diagram is recommended.

5.8 TUR of TaT1 bladder tumours

The goal of the TUR in TaT1 bladder tumours is to make the correct diagnosis and remove all visible lesions.

The strategy of resection depends on the size of the lesion. Small tumours (< 1 cm) can be resected *en bloc*, the specimen contains the complete tumour plus a part of the underlying bladder wall. Some experts believe that deep resection is not necessary in small, apparently low-grade lesions with a previous history of TaG1 tumour. Larger tumours should be resected separately in fractions, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. The specimens from different fractions must be referred to the pathologist in separate containers to enable him/her to make a correct diagnosis. Cauterisation should be avoided as much as possible during TUR to prevent tissue destruction.

Complete and correct TUR is essential to achieve a good prognosis (78). It has been confirmed that absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease and early recurrence (79) (LE: 2).

5.9 Bladder and prostatic urethral biopsies

Carcinoma *in situ* can present as a velvet-like, reddish area that is indistinguishable from inflammation, or it might not be visible at all. It can be present as an isolated lesion without exophytic tumour, or it can accompany TaT1 tumours.

When abnormal areas of urothelium are seen, it is advised to take 'cold cup' biopsies or biopsies with a resection loop. Biopsies from normal-looking mucosa, so-called random biopsies (R-biopsies), should be performed in patients with positive urinary cytology and absence of visible tumour in the bladder. It is recommended to take R-biopsies from the trigone, bladder dome and from right, left, anterior and posterior bladder walls.

In patients with TaT1 tumours, R-biopsies are not routinely recommended. The likelihood of detecting CIS, especially in low-risk tumours, is extremely low (< 2%) (80) (LE: 2a). Cold cup biopsies from normal-looking mucosa should be performed when cytology is positive or when exophytic tumour has a non-papillary appearance. Material obtained by random or directed biopsies must be sent for pathological assessment in separate containers. In CIS, the coherence and adherence of epithelial cells is decreased, and this feature often results in denuded biopsies when taken by cold cup or a resection loop (81).

Involvement of the prostatic urethra and ducts in male patients with non-muscle-invasive bladder cancer has been reported. Although the exact risk of prostatic urethra or ducts involvement is not known, it seems to be higher if tumour is located on the trigone or bladder neck, in the presence of bladder CIS and multiple tumours (82,83) (LE: 3). In these cases and when cytology is positive, with no evidence of tumour in the bladder, or when abnormalities of prostatic urethra are visible, biopsies of the prostatic urethra are recommended. The biopsy is taken from abnormal areas and from the precollicular area (between 5 and 7 o'clock position) using a resection loop.

5.10 Photodynamic diagnosis (fluorescence cystoscopy)

As a standard procedure, cystoscopy and TUR are performed using white light. However, the use of white light can lead to missing lesions that are present but not visible. Photodynamic diagnosis (PDD) is performed using violet light after intravesical instillation of 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL). It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures for detection of malignant tumours, particularly for CIS (84-86) (LE: 2a). The additional detection rate with PDD was 20% for all tumours and 23% for CIS in a cumulative analysis of prospective trials (87). However, false-positivity can be induced by inflammation or recent TUR, and during the first 3 months after BCG instillation (88).

The benefit of ALA fluorescence-guided TUR for recurrence-free survival has been demonstrated in several small, randomised clinical trials (89-91). Cumulative analysis of three trials has shown that the recurrence-free survival was 15.8-27% higher at 12 months and 12-15% higher at 24 months in the fluorescence-guided TUR groups compared to the white light cystoscopy alone groups (87) (LE: 2) However, a large Swedish study could not detect any advantage in using ALA fluorescence-guided TUR routinely in all patients with non-muscle-invasive bladder cancer (92). A recent large, multicentre, prospective randomised trial that compared HAL fluorescence-guided TUR with standard TUR reported an absolute reduction of no more than 9% in the recurrence rate within 9 months in the HAL arm (93) (LE: 1b).

The value of fluorescence cystoscopy for improvement of the outcome in relation to progression rate or survival remains to be demonstrated.

Photo-dynamic diagnosis is most useful for detection of CIS, and therefore, it should be restricted to those patients who are suspected of harbouring a high-grade tumour, e.g. for biopsy guidance in patients with positive cytology or with a history of high-grade tumour. Because of conflicting data on recurrence rate this panel restricts the indication for PDD more than experts in a recently published review (94).

The additional costs of the equipment and instillation for PDD should be taken into account.

5.11 Second resection

The significant risk of residual tumour after initial TUR of TaT1 lesions has been demonstrated (78,95) (LE: 2a). Persistent disease after resection of T1 tumours has been observed in 33-53% of patients (95-100).

Moreover, the tumour is often under-staged by initial resection. The likelihood that a T1 tumour has been under-staged and muscle-invasive disease is detected by second resection ranges from 4 to 25%. This risk has increased up to 50% in some cystectomy series, although these studies have only enrolled selected patients (96,101,102) (LE: 2a). Treatment of a TaT1 high-grade tumour and a T2 tumour is completely different; therefore, correct staging is important.

A second TUR should be considered when the initial resection is incomplete, for example, when multiple and/or large tumours are present, or when the pathologist has reported that the specimen contains no muscle tissue (TaG1 excluded). Furthermore, a second TUR should be performed when a high-grade or T1 tumour has been detected at initial TUR (103). It has been demonstrated that a second TUR can increase the recurrence-free survival (98,99,104) (LE: 2a). There is no consensus about the strategy and timing of second TUR. Most authors recommend resection at 2-6 weeks after initial TUR. The procedure should include resection of the primary tumour site.

5.12 Pathological report

Pathological investigation of the specimen obtained by TUR and biopsies is an essential step in the diagnosis of bladder cancer. The pathological report should specify the grade of the lesion(s) and the depth of tumour invasion into the bladder wall, and should give information about whether the lamina propria and sufficient muscle are present in the specimen (104).

Essential for correct pathological assessment is the high quality of resected tissue. The presence of sufficient muscle is necessary for correct assignment of T category. Close cooperation between urologists and pathologists is recommended.

5.13 Recommendations for primary assessment of non-muscle invasive bladder tumours

	GR
The renal and bladder US may be used during initial work-up in patients with haematuria.	C
At the time of initial diagnosis of bladder cancer CT urography or IVU should be performed only in selected cases (e.g. tumours located in the trigone).	B
Cystoscopy is recommended in all patients with symptoms suggestive of bladder cancer. It cannot be replaced by cytology nor by any other non-invasive test.	A
Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended.	C
Voided urine cytology or urinary markers are advocated to predict high grade tumour before TUR.	C
It is recommended to perform TUR in one piece for small papillary tumours (< 1 cm), including part from the underlying bladder wall.	B
It is recommended to perform TUR in fractions (including muscle tissue) for tumours over 1 cm in diameter.	B
It is recommended to take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (trigone, bladder dome and from right, left, anterior and posterior bladder walls) are recommended only when cytology is positive or when exophytic tumour has a non-papillary appearance.	C
Biopsy of the prostatic urethra is recommended for cases of bladder neck tumour, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection. The biopsy should be taken from the precollicular area between 5 and 7 o'clock using a resection loop.	C
If equipment is available, fluorescence-guided (PDD) biopsy should be performed when bladder CIS is suspected (e.g. positive cytology, recurrent tumour with previous history of a high-grade lesion).	B
A second TUR should be performed at 2-6 weeks after initial resection when the latter is incomplete (in large and multiple tumours, no muscle in the specimen), or when an exophytic high-grade and/or T1 tumour is detected.	A
The pathological report should specify the grade, depth of tumour invasion, and whether the lamina propria and sufficient muscle are present in the specimen.	A

CIS = carcinoma in situ; CT = computed tomography; IVU = intravenous urography; PDD = photodynamic diagnosis; TUR = transurethral resection.

6. PREDICTING RECURRENCE AND PROGRESSION

6.1 TaT1 tumours

The classic way to categorise patients with TaT1 tumours is to divide them into risk groups based on prognostic factors derived from multivariate analyses. Using such a technique, it has been proposed to divide patients into low-risk, intermediate-risk and high-risk groups (105). When using these risk groups, however, no distinction is usually drawn between the risk of recurrence and progression. Although prognostic factors

indicate a high risk for recurrence, the risk of progression might still be low, and other tumours might have a high risk of recurrence and progression.

In order to predict separately the short-term and long-term risks of recurrence and progression in individual patients, the European Organization for Research and Treatment of Cancer (EORTC)- Genitourinary (GU) group has developed a scoring system and risk tables (106). The basis for these tables is the EORTC database, which provides individual patient data for 2,596 patients diagnosed with TaT1 tumours, who were randomised in seven EORTC-GU group trials. Patients with CIS alone are not included. Seventy-eight percent of patients have received intravesical treatment, mostly chemotherapy. However, they have not undergone a second TUR or received maintenance BCG. The scoring system is based on the six most significant clinical and pathological factors:

- number of tumours;
- tumour size;
- prior recurrence rate;
- T-category;
- presence of concurrent CIS;
- tumour grade.

Table 6 illustrates the weights applied to various factors for calculating the total scores for recurrence and progression. Table 7 shows the total scores stratified, as in the original article (106), into four categories that reflect various probabilities of recurrence and progression at 1 and 5 years. By combination of two of the four categories for recurrence and progression, the EAU working group suggests the use of a three-tier system that defines low-, intermediate- and high-risk groups for recurrence and progression (*as shown in the rightmost column in Table 7*).

Table 6: Weighting used to calculate recurrence and progression scores

Factor	Recurrence	Progression
Number of tumours		
Single	0	0
2-7	3	3
≥ 8	6	3
Tumour diameter		
< 3 cm	0	0
≥ 3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4
Concurrent CIS		
No	0	0
Yes	1	6
Grade (WHO 1973)		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

CIS = carcinoma in situ; WHO = World Health Organization.

Table 7: Probability of recurrence and progression according to total score

Recurrence score	Probability of recurrence at 1 year		Probability of recurrence at 5 years		Recurrence risk group
	%	(95% CI)	%	(95% CI)	
0	15	(10-19)	31	(24-37)	Low risk
1-4	24	(21-26)	46	(42-49)	Intermediate risk
5-9	38	(35-41)	62	(58-65)	
10-17	61	(55-67)	78	(73-84)	High risk

Recurrence score	Probability of progression at 1 year		Probability of progression at 5 years		Progression risk group
	%	(95% CI)	%	(95% CI)	
0	0.2	(0-0.7)	0.8	(0-1.7)	Low risk
2-6	1	(0.4-1.6)	6	(5-8)	Intermediate risk
7-13	5	(4-7)	17	(14-20)	High risk
14-23	17	(10-24)	45	(35-55)	

Note: Electronic calculators for Tables 6 and 7 are available at http://www.eortc.be/tools/bladdercalculator/.

The scoring model for BCG-treated patients that predicts the short- and long-term risks of recurrence and progression has recently been presented by the Club Urológico Español de Tratamiento Oncológico (CUETO) (Spanish Urological Oncology Group). It is based on analysis of 1,062 patients from four CUETO trials that compared different intravesical BCG treatments. Patients received 12 instillations during 5-6 months. No immediate postoperative instillation or second TUR were performed in these patients. The scoring system is based on evaluation of seven prognostic parameters:

- Patients' sex;
- Patients' age;
- Recurrence status;
- Number of tumours;
- T category;
- Associated CIS;
- Tumour grade.

Using these tables, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression probabilities, it is lower only in high-risk patients (107). The lower risks in the CUETO tables may be attributed to using a more effective instillation therapy in the individual studies on which the CUETO tables are based. The validation of the EORTC scoring system in an independent patient population with long-term follow-up has confirmed its prognostic value (108).

6.2 CIS

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease (109). Unfortunately, there are no reliable prognostic factors that can be used to predict the course of the disease and specify the most dangerous cases. The publications are based on a retrospective analysis of small series of patients and their conclusions are not homogeneous. Some studies have reported worse prognosis in concurrent CIS and T1 tumours compared to primary CIS (110,111) and in extended CIS (112) (LE: 3).

Various publications have shown that the response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by bladder cancer (113-116). Approximately 10-20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of non-responders (113-115) (LE: 2).

7. ADJUVANT TREATMENT

7.1 Intravesical chemotherapy

Although state-of-the-art TUR by itself can eradicate a TaT1 tumour completely, these tumours recur in a high percentage of cases and progress to muscle-invasive bladder cancer in a limited number of cases. The high variability in the 3-month recurrence rate indicates that TUR is incomplete or provokes recurrences in a high percentage of patients (78). It is therefore necessary to consider adjuvant therapy in all patients. The absolute risks of recurrence and progression do not always indicate the risk at which a certain therapy is optimal. The choice of therapy may be considered differently according to what risk is acceptable for the individual patient and the urologist.

7.1.1 One, immediate, postoperative intravesical instillation of chemotherapy

In a meta-analysis of seven randomised trials (1,476 patients with a median follow-up of 3.4 years), one immediate instillation of chemotherapy after TUR significantly reduced recurrence rate compared to TUR alone (LE: 1a) (117). In absolute values, the reduction was 11.7% (from 48.4% to 36.7%), which implies a 24.2% decrease in the corresponding relative risk. The majority of patients (> 80%) in the meta-analysis had a single tumour, but an almost significant and even greater reduction in recurrence was noted among the limited number of patients with multiple tumours. The efficacy of the single instillation has been confirmed also by two recently published studies (118,119). In one of these (119), the benefit was mainly seen in primary and single tumours and was in these tumour categories even greater than the 11.7%. By stratification according to EORTC recurrence scores, the benefit was observed in patients with scores 0-2, but not with scores ≥ 3. However, the study was not sufficiently powered for subgroup analyses. Despite stratification at randomisation, no separate analysis was made for primary or recurrent tumours in the other study (118).

No prospective data are available showing that the single instillation significantly reduces recurrence rates in patients with recurrent tumours. Nevertheless, there is significant evidence from one subgroup analysis that an immediate instillation might have an impact on the repeat instillation regimen for treatment of patients who are at intermediate- and high risk of recurrence (120) (LE: 2a). There are no statistically relevant data that address the role of immediate chemotherapy instillation in tumours at high risk of progression before further BCG intravesical treatment.

In summary, one immediate instillation significantly reduces the risk of recurrence in TaT1 bladder tumours. Further studies are required, however, to determine the definitive role of immediate chemotherapy before BCG or further chemotherapy instillations in intermediate- and high-risk groups.

The effect of early instillation can be explained by the destruction of circulating tumour cells immediately after TUR, or as an ablative effect (chemoresection) of residual tumour cells at the resection site. Prevention of tumour cell implantation should be initiated within the first hours after cell seeding. Within a few hours, the cells are implanted firmly and are covered by extracellular matrix (121-124). In all single instillation studies, the instillation was administered within 24 h. Subgroup analysis of one study has shown that, if the first instillation was not given on the same day as TUR, there was a twofold increase in the relative risk of recurrence (120) (LE: 2a). Moreover, a study in which the instillation was not given strictly on the same day did not find any advantage (125). To maximise the efficacy of the immediate instillation, every effort should be made to create flexible practices that allow the instillation to be given when necessary and as early as possible, that is, in the recovery room or even in the operating theatre.

There is no single drug that is superior with regard to efficacy. Mitomycin C, epirubicin and doxorubicin have all shown a beneficial effect (117) (LE: 1a). In one study, gemcitabine plus 24 h bladder irrigation with physiological saline was not superior to irrigation with physiological saline alone (126) (LE: 1b).

The guidelines expert panel recommends early immediate instillation in tumours at low risk of progression (single, primary, papillary lesions) as the only intravesical treatment and in those presumably at intermediate risk, for which a single instillation is considered as the initial stage of further intravesical therapy. In tumours that are presumably at high risk of progression (solid lesions, positive urinary cytology), immediate instillation is an option because it can have a positive impact on recurrence rate through prevention of tumour cell implantation. However, there is no doubt that subsequent BCG intravesical immunotherapy is essential treatment in these patients (see lower).

The immediate post-operative chemotherapy instillation should be omitted in any case of overt or suspected intra- or extraperitoneal perforation, which is most likely to appear in extensive TUR procedures, and in situations with bleeding requiring bladder irrigation. Severe complications have been reported in patients in whom extravasation of the drug occurs (127).

Clear instructions should be given to the nursing staff to control the free flow of the bladder catheter at the end of the instillation. It has been demonstrated that administration of instillation is possible in the majority of cases (128).

*7.1.2 **Additional adjuvant intravesical chemotherapy instillations***

The need for further adjuvant intravesical therapy depends on the patients' prognosis. In patients with a low risk of tumour recurrence (see Table 7), a single immediate instillation reduces the risk of recurrence and is considered as the standard treatment (117) (LE: 1a). No further treatment should be given in these patients before subsequent recurrence. For other patients, however, a single immediate instillation remains an incomplete treatment because the likelihood of recurrence and/or progression is considerable.

The effect of the immediate instillation of chemotherapy occurs during the first and second year (129,130) (LE: 1b). It has been calculated from the data of five randomised trials (130) that the reduction of recurrence lasts for a period of approximately 500 days.

The choice between further chemotherapy or immunotherapy largely depends on the risk that needs to be reduced: recurrence or progression. A combined analysis of EORTC and Medical Research Council data, comparing intravesical chemotherapy to TUR alone, has demonstrated that chemotherapy prevents recurrence but not progression (131) (LE: 1a). The efficacy of intravesical chemotherapy in reducing the risk of tumour recurrence has been confirmed by two other meta-analyses in primary (132) and recurrent tumours (133).

It is still controversial how long and how frequently instillations of intravesical chemotherapy have to be given. From a systematic review of the literature of randomised clinical trials, which has compared different schedules of intravesical chemotherapy instillations, one can only conclude that the ideal duration and intensity of the schedule remains undefined because of conflicting data (134). Nevertheless, the available evidence does not support any treatment longer than 1 year.

*7.1.3 **Optimising intravesical chemotherapy***

One randomised trial has demonstrated that adapting urinary pH, decreasing urinary excretion, and buffering the intravesical solution reduce the recurrence rate (135) (LE: 1b).

Another randomised trial has documented that concentration is more important than duration of the treatment (136) (LE: 1b). In view of these data, which need confirmation, it seems advisable to ask the patient not to drink on the morning before instillation, and to dissolve the drug in a buffered solution at optimal pH.

7.2 Intravesical BCG immunotherapy

*7.2.1 **Efficacy of BCG***

Several meta-analyses have addressed important questions concerning the efficacy of BCG in non-muscle invasive bladder tumours. Four meta-analyses have confirmed that BCG after TUR is superior to TUR alone or TUR and chemotherapy for prevention of recurrence of non-muscle invasive tumours (137-140) (LE: 1a). Since the publication of these meta-analyses, three randomised studies of intermediate- and high-risk tumours have been presented. In these studies, BCG was compared with the combination of epirubicin and interferon (141), mitomycin C (MMC) (142) or epirubicin (143) alone. All of these studies have confirmed the superiority of BCG for prevention of tumour recurrence. It has been shown that the effect was long lasting (142,143) and was also observed in a separate analysis of patients with tumours at intermediate risk (143).

One recently published meta-analysis (144) has evaluated the individual data from 2,820 patients enrolled in nine randomised studies that have compared MMC versus BCG. In the trials with BCG maintenance, a 32% reduction in the risk of recurrence for BCG compared to MMC was found ($p < 0.0001$), whereas there was a 28% increase in the risk of recurrence ($p = 0.006$) for patients treated with BCG in the trials without BCG maintenance.

Two meta-analyses have demonstrated that BCG therapy prevents, or at least delays, the risk of tumour progression (145,146) (LE: 1a). A meta-analysis carried out by the EORTC-GU group has evaluated data from 4,863 patients enrolled in 24 randomised trials. A total of 3,967 (81.6%) patients had only papillary tumours and 896 (18.4%) had primary or concurrent CIS. Five different BCG strains were used, and in 20 out of the 24 trials, some form of BCG maintenance was used. In four trials only, a 6-week induction course was used. Based on a median follow-up of 2.5 years and a maximum of 15 years, 260 out of 2,658 patients (9.8%) on BCG progressed compared to 304 out of 2,205 (13.8%) in the control groups (TUR alone, TUR plus intravesical chemotherapy, or TUR plus other immunotherapy). This shows a reduction of 27% in the odds of progression with BCG maintenance treatment ($p = 0.0001$). The size of the reduction is similar in patients with TaT1 papillary tumours and in those with CIS (146). A recent randomised study with long-term observation has demonstrated significantly fewer distant metastases and better overall- and disease-specific survival in patients treated with BCG compared to epirubicin (143) (LE: 1b). On the contrary, a meta-analysis of individual patient data was not able to confirm any statistically significant difference between MMC and BCG for progression, survival and cause of death (144). In summary, in spite of these conflicting results, the majority of data was able to show the reduction in the risk of progression in tumours at high and intermediate risk if the BCG including maintenance schedule was used.

Two other meta-analyses have suggested a possible bias in favour of BCG by the inclusion of patients who were previously treated with intravesical chemotherapy (147,148). In the most recent meta-analysis,

however, BCG maintenance was more effective than MMC also in patients who were previously treated with chemotherapy (144).

7.2.2 ***Optimal BCG schedule***

For optimal efficacy, BCG must be given in a maintenance schedule (140,144-146) (LE: 1a). In the EORTC-GU group meta-analysis, only patients who received maintenance BCG benefited. In the four trials in which no maintenance was given, no reduction in progression was observed. In the 20 trials in which some form of BCG maintenance was given, a reduction of 37% in the odds of progression was observed ($p = 0.00004$). The meta-analysis was unable to determine which BCG maintenance schedule was the most effective (146). In their meta-analysis, Böhle et al. have concluded that at least 1 year of maintenance BCG is required to obtain the superiority of BCG over MMC for prevention of recurrence or progression (140,145). Although some modifications have been tried, induction BCG instillations are classically given according to the empirical 6-weekly induction schedule that was introduced by Morales in 1976 (149). However, many different maintenance schedules have been used, ranging from a total of 10 instillations given in 18 weeks, to 27 instillations over 3 years (150). The optimal number of induction instillations and the optimal frequency and duration of maintenance instillations remain unknown (151).

7.2.3 ***Optimal dose of BCG***

To reduce BCG toxicity, a number of authors have proposed one-third and one-quarter dose instillations of BCG. Comparing one-third dose to full-dose BCG in 500 patients, CUETO has found no overall difference in efficacy. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours (152,153) (LE: 1b). Although fewer patients have reported toxicity with the reduced dose, the incidence of severe systemic toxicity has been similar in the standard- and reduced-dose groups. The same Spanish group has shown in a prospective randomised trial that one-third of the standard dose of BCG might be the minimum effective dose in intermediate-risk tumours. A further reduction to one-sixth dose resulted in a decrease in efficacy for prevention of recurrence with no decrease in toxicity (154).

7.2.4 ***BCG toxicity***

Assuming that maintenance therapy is necessary for optimal efficacy, the issue of BCG toxicity becomes more relevant. As a result of the more pronounced side effects of BCG compared to intravesical chemotherapy, there is still reluctance about the use of BCG. Deaths due to BCG sepsis and the high frequency of BCG-induced cystitis and allergic reactions have compromised its use (155). However, with increased experience in using BCG, the side effects now appear to be less prominent. Serious side effects are encountered in < 5% of patients and can be effectively treated in virtually all cases (155) (LE: 1b). Major complications can appear after systemic absorption of the drug. Thus, BCG should not be administered during the first 2 weeks after TUR, in patients with macroscopic haematuria or urinary tract infection, or after traumatic catheterisation. It should not be used in immunocompromised patients (immunosuppression, HIV) (156).

The management of side-effects after BCG should reflect their type and grade. Recommendations for individual situations were provided by the International Bladder Cancer Group and by a Spanish group (157,158). Before applying intravesical BCG therapy the urologist should be aware how to treat BCG-induced complications.

7.2.5 ***Indications for BCG***

Although BCG is a very effective treatment, there is a consensus that not all patients with non-muscle-invasive bladder cancer should be treated with BCG due to the risk of toxicity. Ultimately, the choice of treatment depends upon the patients' risk of recurrence and progression (*see* Table 7). The use of BCG does not alter the natural course of tumours at low risk of recurrence (*see* Table 7), and could be considered to be over-treatment for this patient category. In patients with tumours at high risk of progression, for whom cystectomy is not carried out, BCG including at least 1 year maintenance is indicated. In patients at intermediate or high risk of recurrence and intermediate risk of progression, BCG with 1 year maintenance is more effective than chemotherapy for prevention of recurrence; however, it has more side effects than chemotherapy. For this reason both BCG with maintenance and intravesical chemotherapy remain an option. The final choice should reflect the individual patients' risk of recurrence and progression and efficacy and side effects of each treatment modality.

7.3 Specific aspects of treatment of CIS

7.3.1 ***Treatment strategy***

If concurrent CIS is found in association with muscle-invasive bladder cancer, therapy is determined according to the invasive tumour. The detection of CIS with TaT1 tumours increases the risk of recurrence and

progression of TaT1 tumours (106,107) and further treatment is mandatory. The treatment strategy is generally based on the criteria that are summarised in Sections 7.1, 7.2, 7.4 and Chapter 8.

Carcinoma *in situ* cannot be cured by an endoscopic procedure only. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or radical cystectomy (LE: 2). No consensus exists about whether conservative therapy (intravesical BCG instillations) or aggressive therapy (cystectomy) should be done, especially when there are concurrent high-grade papillary tumours. There has been a lack of randomised trials of instillation therapy and early cystectomy as immediate primary treatment. Tumour-specific survival rates after early cystectomy for CIS are excellent, but as many as 40-50% of patients might be over-treated (3).

7.3.2 ***Cohort studies***

In retrospective evaluations of patients with CIS, a complete response rate of 48% was achieved with intravesical chemotherapy and 72-93% with BCG (109-112,159) (LE: 2). Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence (112,150,159,160).

7.3.3 ***Prospective randomised trials***

Unfortunately, there have been few randomised trials in patients with CIS alone. Most trials have included patients with either papillary tumours or CIS, which has resulted in only a small number of CIS patients being entered. Thus, the power to detect differences of treatment results has been low and the reliability of the conclusions is limited (3).

A meta-analysis of clinical trials that has compared intravesical BCG to intravesical chemotherapy (MMC, epirubicin or adriamycin) in patients with CIS has shown a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG (OR = 0.41, p = 0.0001). In trials that have compared BCG with MMC, the long-term benefit of BCG was smaller, but BCG was superior to MMC in trials with BCG maintenance (OR = 0.57, p = 0.04) (161).

In an EORTC-GU group meta-analysis of tumour progression, in a subgroup of 403 patients with CIS, BCG reduced the risk of progression by 35% as compared to intravesical chemotherapy or different immunotherapy (OR = 0.65, 95% CI = 0.36-1.16, p = 0.10) (146) (LE: 1b). There has been no single trial that has demonstrated superiority of combined BCG and MMC over BCG alone (162) (LE: 1).

In summary, as compared to chemotherapy, treatment of patients with CIS using BCG increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression (LE: 1a).

7.3.4 ***Treatment of extravesical CIS***

Patients with CIS are at high risk of extravesical involvement: in the upper urinary tract and in the prostatic urethra. Solsona et al have found that 87 of 138 patients (63%) with CIS developed extravesical involvement initially or during follow-up (163). Patients with extravesical involvement had worse survival than those with bladder CIS alone (163) (LE: 3).

In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts (3). These situations should be distinguished from tumour invasion into the stroma of the prostate, which is staged as T4a, and for which, immediate cystoprostatectomy is mandatory. Patients with CIS in the epithelial lining of the prostatic urethra can be treated by intravesical instillations of BCG. TUR of the prostate can improve the contact of BCG with the prostatic urethra (3,164,165) (LE: 3). In patients with prostatic duct involvement, the data are insufficient to provide clear treatment recommendations. As no conclusive results have been attained with regard to the use of conservative therapy, radical surgery should be considered in these patients (165) (LE: 3).

The treatment of CIS that involves the upper urinary tract is discussed in the upper urinary tract guidelines.

7.4 Treatment of failure of intravesical therapy

7.4.1 ***Failure of intravesical chemotherapy***

Patients with non-muscle invasive recurrence of urothelial bladder carcinoma after intravesical chemotherapy can profit from BCG instillations (147) (LE: 1a).

7.4.2 ***Failure of intravesical BCG immunotherapy***

Treatment with BCG is considered to have failed in following situations:

a. Whenever muscle-invasive tumour is detected during follow-up.

b. If high-grade, non-muscle-invasive tumour is present at both 3 and 6 months (166). In patients with tumour present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases, both in patients with papillary tumours and CIS (37,166), but with increasing risk of progression

(167,168).

c. Any worsening of the disease under BCG treatment, such as a higher number of recurrences, higher T stage or higher grade, or appearance of CIS, in spite of an initial response (LE: 3).

Changing from BCG to intravesical chemotherapy, device-assisted chemotherapy instillations, or additional interferon α-2b immunotherapy can yield responses in selected cases with non-muscle-invasive BCG treatment failure (169-178). However, experience is limited and these strategies are considered experimental. As a result of the high risk of development of muscle-invasive tumour in these patients (166-168) (LE: 3), cystectomy is strongly advocated upon early BCG failure in fit patients.

Patients with a recurrence at > 1 year after completion of BCG therapy can be treated according to the risk classification (*See Tables 6, 7 and 8*) (169).

7.5 Recommendations for adjuvant therapy in TaT1 tumours and for therapy of CIS

	GR
The type of intravesical therapy should be based on the risk groups shown in Table 7.	A
In patients with TaT1 tumours at low risk of recurrence and progression, one immediate instillation of chemotherapy is recommended as the complete adjuvant treatment.	A
In patients with TaT1 tumours at intermediate or high risk of recurrence and intermediate risk of progression, one immediate instillation of chemotherapy should be followed by a minimum 1 year of BCG treatment, or by further instillations of chemotherapy.	A
If chemotherapy is given, it is advised to use the drug at its optimal pH and to maintain the concentration of the drug during instillation by reducing fluid intake. The optimal schedule and the duration of the chemotherapy instillations remain unclear, but it should be given no more than 12 months.	B
In patients with TaT1 tumours at high risk of progression, intravesical BCG for at least 1 year is indicated.	A
In patients with bladder CIS, intravesical BCG for at least 1 year is indicated.	A
In patients with CIS in the epithelial lining of the prostatic urethra, TUR of the prostate followed by intravesical instillations of BCG could be an option.	C
Immediate radical cystectomy may be offered to patients at highest risk of tumour progression.	C
In patients with BCG failure, cystectomy is indicated.	B

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; TUR = transurethral resection.

Table 8: Treatment recommendations in TaT1 tumours according to risk stratification

Risk category	Low	Intermediate	High
Recurrence	One immediate instillation of chemotherapy	One immediate instillation of chemotherapy, followed by further instillations, either chemotherapy or a minimum 1 year of BCG (the final choice is determined by the risk of tumour progression)	One immediate instillation of chemotherapy, followed by further instillations, either chemotherapy or a minimum of 1 year of BCG (the final choice is determined by the risk of tumour progression)
Progression	One immediate instillation of chemotherapy (it can be followed by further chemotherapy instillations if the patients has at the same time an intermediate risk of recurrence)	One immediate instillation of chemotherapy, followed by a minimum of 1 year of BCG or further chemotherapy instillations	Intravesical BCG for at least 1 year, or immediate cystectomy

BCG = bacillus Calmette-Guérin.

8. CYSTECTOMY FOR NON-MUSCLE-INVASIVE BLADDER CANCER

Some experts consider it is reasonable to propose immediate cystectomy to those patients with non-muscle-invasive tumour who are at high risk of progression. According to the risk tables of the EORTC (*see* Tables 6 and 7) these are:

- multiple recurrent high-grade tumours;
- high-grade T1 tumours;
- high-grade tumours with concurrent CIS.

With these patients, it is recommended to discuss both treatment options: immediate cystectomy and conservative treatment with BCG instillations. Patients should be informed about the benefits and risks of both approaches.

Cystectomy is advocated in patients with non-muscle-invasive tumours with BCG treatment failure, as mentioned above. Delay of cystectomy in these patients might lead to decreased disease-specific survival (179). In patients in whom cystectomy is performed at the time of pathological non-muscle-invasive disease, the 5-year disease-free survival exceeds 80% (180-185).

9. FOLLOW-UP OF PATIENTS WITH NON-MUSCLE-INVASIVE BLADDER TUMOURS

As a result of the risk of recurrence and progression, patients with TaT1 bladder tumours need to be followed; however, the frequency and duration of cystoscopy and imaging should reflect the individual patients' degree of risk. Using risk tables (see Tables 6 and 7), we are able to predict the short-term and long-term risks of recurrence and progression in individual patients, and can adapt the follow-up schedule accordingly (106). By planning the follow-up schedule the following aspects should be considered:

a. *The prompt detection of muscle-invasive and high-grade non-muscle-invasive recurrence is crucial because a delay in diagnosis and therapy can be life-threatening to the patient.*

b. *Tumour recurrence in the low-risk group is nearly always low stage and low grade.*
Small, non-invasive (Ta), low-grade papillary recurrence does not present an immediate danger to the patient, and early detection is not essential for successful therapy (186-193) (LE: 2b). In these patients, fulguration of small papillary recurrences on an outpatient basis could be a safe treatment option that reduces the therapeutic burden. (194) (LE: 3). Some authors even defend temporary surveillance (192,193,195).

c. *The result of the first cystoscopy after TUR at 3 months is a very important prognostic indicator for recurrence and progression* (106,168,196,197) (LE: 1a). The first cystoscopy should thus **always** be performed 3 months after TUR in all patients with TaT1 bladder tumour.

d. *The risk of upper urinary tract recurrence increases in patients with multiple and high risk tumours* (42) (LE: 3).

As there has not been presented any non-invasive method that could replace endoscopy, the follow-up is based on regular cystoscopies (see 5.5). There has been a lack of randomised studies that have investigated the possibility of safely reducing frequency of follow-up cystoscopies. The following recommendations are therefore based only on retrospective experience.

9.1 Recommendations for follow-up in patients after TUR of non-muscle invasive bladder cancer

	GR
Patients with TaT1 tumours at low risk of recurrence and progression should have a cystoscopy at 3 months. If negative, the following cystoscopy is advised 9 months later, and then yearly for 5 years.	C
Patients with TaT1 tumours at high risk of progression and those with CIS should have a cystoscopy and urinary cytology at 3 months. If negative, the following cystoscopy and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly. Yearly imaging of the upper tract is recommended.	C
Patients with TaT1 tumours at intermediate risk of progression (about one-third of all patients) should have an in-between follow-up scheme using cystoscopy and cytology, which is adapted according to personal and subjective factors.	C
During follow-up in patients with positive cytology and no visible tumour in the bladder, R-biopsies or biopsies with PDD (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	B

CIS = carcinoma in situ; PDD = photodynamic diagnosis.

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11. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

5-ALA	5-aminolaevulinic acid
BCG	bacillus Calmette-Guérin
CIS	carcinoma *in situ*
CT	computed tomography
CUETO	Club Urológico Español de Tratamiento Oncológico (Spanish Oncology Group)
EAU	European Association of Urology
EORTC	European Organization for Research and Treatment of Cancer
FISH	fluorescence *in situ* hybridisation
GR	grade of recommendation
HAL	hexaminolaevulinic acid
ISUP	International Society of Urological Pathology
IVU	intravenous urography
LE	level of evidence
MM	mitomycin C
NMIBC	non-muscle invasive bladder cancer
NVP	negative predictive value
PDD	photodynamic diagnosis
PUNLMP	papillary urothelial neoplasms of low malignant potential
RCT	randomised controlled trials
TCC	transitional cell carcinoma
TNM	tumour, node, metastasis
TUR	transurethral resection
UICC	Union International Contre le Cancer
US	ultrasonography
WHO	World Health Organization

Conflict of interest

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